

Remarks

Applicants request reconsideration of the above-referenced patent application.

I. Amendments to Specification

In accordance with 37 CFR §1.78 and MPEP §202.01, the paragraph bridging lines 6-8 on page 1 has been amended to correct the citation of one of the patent applications to which this patent application is claiming priority.

II. Claim Amendments

This amendment adds new claims 8-16. Thus, claims 1-16 are pending. Applicants have amended claims 1-7. The claims, including the amendments and new claims, are shown in the previous section. Applicants submit that the amendments do not introduce any new matter. Specifically:

Claim 1 has been amended to list all the “X” definitions together. Applicants submit that this makes claim 1 easier to read.

The variable “R⁸” is used in all four “X” structures in claim 1. To make claim 1 easier to read, the “R⁸” in the second structure has been replaced with “R^{8A}”, the “R⁸” in the third structure has been replaced with “R^{8B}”, and the “R⁸” in the fourth structure has been replaced with “R^{8C}”. The corresponding text definitions for each “X” have similarly been amended.

The variable “R⁹” is used in the first, third, and fourth “X” structures in claim 1. To make claim 1 easier to read, the “R⁹” in the third structure has been replaced with “R^{9B}”, and the “R⁹” in the fourth structure has been replaced with “R^{9C}”. The corresponding text definitions for each “X” have similarly been amended.

The variable “R¹” is used in the first, third, and fourth “X” structures in claim 1. To make claim 1 easier to read, the “R¹” in the third structure has been replaced with “R^{1B}”, and the “R¹” in the fourth structure has been replaced with “R^{1C}”. The corresponding text definitions for each “X” have similarly been amended.

Claims 2, 3, 5, and 6 have been amended to expressly encompass isomers, enantiomers, tautomers, racemates, and polymorphs of the recited compounds; and pharmaceutically acceptable salts of the recited compounds and their isomers, enantiomers, tautomers, racemates,

and polymorphs. This amendment makes claims 2, 3, 5, and 6 more consistent with claim 1, *i.e.*, the claim from which claims 2, 3, 5, and 6 depend.

Claim 5 has been amended to remove “preventing”, as suggested by the Examiner on page 3 of the Office action.

Claims 5 and 6 have been amended to characterize the treated condition as a pathological condition. This amendment is supported by Applicants' specification at, for example, page 13, lin10-11.

Claim 6 has been amended to characterize the condition as mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor. This amendment is support by Applicants' specification at, for example, page 6, lines 11-13.

Claim 7 has been amended to expressly characterize the treated angiogenesis as being tumor angiogenesis. This amendment is supported by Applicants' specification at, for example, 13, lines 10-14.

New claims 8-10 are supported by Applicants' specification at, for example, claim 5, as originally filed; as well as the support listed above for the amendments to claim 5.

New claims 11, 13, and 15 are supported by Applicants' specification at, for example, claim 6, as originally filed; as well as the support listed above for the amendments to claim 6.

New claims 12, 14, and 16 are supported by Applicants' specification at, for example, claim 7, as originally filed; as well as the support listed above for the amendments to claim 7.

Other amendments rephrase the claims, remove redundancies or unnecessary terms, or correct grammatical or obvious errors. Applicants submit that such amendments are permissible under MPEP §2163.07.

Applicants reserve the right to pursue any canceled subject matter and/or any other subject matter disclosed in this application in one or more later-filed divisional and/or continuation applications.

III. Response to rejection of claim 5 under 35 U.S.C. §101 and 35 U.S.C. §112 (first paragraph)

Claim 5 has been rejected under 35 U.S.C. §101 for lacking utility and 35 U.S.C. §112 (first paragraph) for lacking enablement. Applicants request withdrawal of this rejection. This rejection appears to be based on two concerns:

- A. The first concern relates to claim 5 being directed to “preventing” in addition to “treating”. Claim 5 has been amended to delete “preventing”, as suggested by the Examiner. Applicants submit that this amendment moots the Examiner’s concern..
- B. The second concern relates to claim 5 encompassing the inhibition of healthy angiogenesis. Claim 5, as amended, characterizes the treated condition as pathological condition. Applicants submit that this amendment moots the Examiner’s concern.

Applicants note that these amendments have simply been made to expedite prosecution of this patent application. Applicants do not make any further representation as to the merits of this rejection.

IV. Response to rejection of claim 5 under 35 U.S.C. §112 (first paragraph)

Claim 5 has been rejected under 35 U.S.C. §112 (first paragraph) for introducing new matter as to the term “integrin receptors”. Applicants request withdrawal of this rejection. Support for this term may be found in Applicants’ specification at, for example, page 6, lines 11-13:

[t]he present invention further provides for methods for treating or preventing conditions mediated by the $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ receptors in a mammal in need of such treatment

V. Response to rejection of claims 5-7 under 35 U.S.C. §112 (first paragraph)

Claims 5-7 have been rejected under 35 U.S.C. §112 (first paragraph) for lacking enablement as to the entire scope of the claims. Applicants request withdrawal of this rejection.

Claims 5 has been rejected for lacking enablement as to the scope of the recited pathological conditions. At the outset, it should be noted that claim 5 has been amended to

remove "preventing". Thus, claim 5, as amended, is directed to compositions useful for treating pathological conditions mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor in a mammal. This claim stems from Applicants' discovery that the recited compounds in claim 1 generally antagonize $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin in a mammal, and therefore can be used to treat pathological conditions mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor. The Office action appears to be requiring that claim 5 be limited to only those diseases that were known in the prior art to be mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor. Such a limitation would be arbitrary. Applicants cannot be required to recite every possible pathological condition that can be treated by the compositions of claim 5, nor can Applicants be required to provide data or citations to corroborate the effectiveness of such compositions toward each possible condition. Such a requirement would place an unfair burden on Applicants to patent the entire scope of their invention. Applicants have defined the recited pathological condition as being mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor. Applicants submit that this adequately defines the condition. This is particularly true, given Applicants' disclosure. Specifically:

- A. Applicants have provided adequate disclosure to enable one skilled in the art to identify pathological diseases mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor.
Applicants have, for example, provided a list of diverse examples of diseases that are mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor. *See, e.g.,* Applicants' specification, page 6, lines 16-21. Applicants also have provided citations that discuss various diseases associated with $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin. *See, e.g.,* Applicants' specification at page 1, line 24 to page 5, line 6. These citations corroborate the effect of $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin with respect to various diseases, and provide additional known details that a skilled artisan may apply when practicing Applicants' invention.
- B. Applicants have provided adequate disclosure to enable one skilled in the art to determine potency and selectivity of a particular compound. Applicants, for example, have provided various assays for assessing integrin potency and selectivity. *See, e.g.,* Applicants' specification at page 74, line 11 to page 79, line 24.

C. Applicants have provided a detailed discussion relating to preparation of the compositions. Applicants specification provides a detailed discussion relating to, for example, factors affecting dosages, example dosages, example modes of administration, and example adjuvants. *See, e.g.,* Applicants' specification at page 34, line 8 to page 37, line 18.

To be enabled under 35 U.S.C. §112 (first paragraph), Applicants' specification must teach those skilled in the art how to make and use the claimed invention without "undue experimentation". *See MPEP §2164.01.* Applicants submit that their specification satisfies this requirement with respect to claim 5. Although preparation of a pharmaceutical composition may, in some instances, require experimentation, Applicants' specification provides guidelines for such experimentation, such as, for example, factors affecting dosages. Moreover, such experimentation, even if deemed complex, is the type that one skilled in the art would typically engage in when preparing pharmaceutical compositions. Thus, Applicants submit that it is not the type that should be construed as "undue experimentation":

[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.

See MPEP §2164.01. In view of the foregoing, Applicants submit that claim 5 must be found to be enabled.

The Office action indicates that Applicants' claim 5 lacks enablement because it is directed to compositions for treating diseases (*e.g.*, various cancers) that are not necessarily mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor. Applicants, however, note that claim 5 is expressly directed to compositions for treating pathological conditions mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor. For example, claim 5 does not necessarily cover compositions for treating all cancers. Instead, claim 5 is directed to compositions for treating cancers that are mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor.

The Office action relies on Nicosia, et al. ("Inhibition of Angiogenesis *In Vitro* by Arg-Gly-Asp-Containing Synthetic Peptide," *American Journal of Pathology*, vol. 138, no. 4, pp. 829-33 (1991)) as supporting the assertion that *in vitro* integrin assays are not a reliable predictor of success for treating an integrin-mediated condition. Applicants respectfully submit that this reliance is misplaced, and that Nicosia et al.'s findings, in fact, demonstrate the opposite.

Specifically, Nicosia et al. predicted (*i.e.*, hypothesized) from an *in vitro* assay that the GRGDS sequence would inhibit angiogenesis even though the GRGES sequence would not. Nicosia et al.'s results confirmed this prediction. In other words, the Nicosia et al. were able to predict their results from an *in vitro* assay.

The Office action also relies on Mundhenke et al. ("Tissue Examination to Monitor Antiangiogenic Therapy: A Phase I Clinical Trial with Endostatin," *Clinical Cancer Research*, vol. 7, pp. 3366-3374 (1991)) as further support for the assertion that *in vitro* integrin assays are not a reliable predictor of success for treating an integrin-mediated condition. Specifically, the Office action cites this reference as showing that endostatin, an angiogenesis inhibitor, is not particularly effective for treating cancer. Applicants respectfully submit that this reliance is misplaced. Mundhenke et al., in fact, expressly state that their study was not designed to test endostatin efficacy:

[i]t is necessary to reinforce the notion that this Phase I trial was not designed to test endostatin efficacy.

See Mundhenke et al., page 3372.

Claims 6 and 7 have been rejected for lacking enablement as to the scope of recited pathological conditions. Claims 6 and 7 characterize the conditions as being mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor. Thus, Applicants submit that these claims are enabled for at least the same reasons as discussed above with respect to claim 5.

Claims 6 and 7 also have been rejected for lacking enablement as to the terms "therapeutically effective" and "inhibiting". Applicants request withdrawal of the rejection. Claim 6 has been amended to more closely track the example language provided on pages 3-4 of the Office action. Specifically, claim 6 has been amended to remove "therapeutically effective amount". Claim 6, as amended, instead characterizes the method as comprising administration of the compound under conditions effective to antagonize $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin. Applicants' submit that this language is enabled. More specifically, Applicants' specification provides a clear definition for "inhibition":

the term "inhibition" of [a] condition refers to slowing, interrupting, arresting or stopping the condition and does not necessarily indicate a total elimination of the condition.

Applicants' specification also provides teachings to determine the conditions effective to antagonize the antagonize $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin. For example, Applicants' specification provides a plethora of example diseases mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor (*see, e.g.*, Applicants' specification at page 13, lines 10-18); citations discussing various diseases associated with $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins (*see, e.g.*, Applicants' specification page 1, line 17 to page 5, line 6); a detailed discussion relating to, for example, factors affecting dosages, example dosages, example modes of administration, and example adjuvants (*see, e.g.*, Applicants' specification at page 34, line 8 to page 37, line 18); and assays to determine potency and selectivity of a particular compound (*see, e.g.*, Applicants' specification at page 74, line 11 to page 79, line 24). Given this disclosure, Applicants submit that claim 6 meets the enablement requirement of 35 U.S.C. §112 (first paragraph).

Claim 7 depends from claim 6. Applicants submit that claim 7 is enabled for at least the same reasons as claim 6.

VI. Response to rejection of claims 1-7 under 35 U.S.C. §112 (second paragraph)

Claims 1-7 have been rejected under 35 U.S.C. §112 (second paragraph) for being indefinite. Applicants request withdrawal of this rejection.

Claim 1 has been rejected for failing to define R⁸ in the case where X is oxygen or sulfur. At the outset, Applicants note that the use of "X" in this rejection appears to be a typographical error, and that the Examiner instead intended to refer to "Y". In the instance where Y is oxygen or sulfur, Applicants submit that claim 1 does define R⁸. Specifically, claim 1 defines R⁸ as forming a ring with R⁹ in that situation. Nevertheless, in an effort to expedite prosecution of this application, claim 1 has been amended to specifically split the R⁸ definition into a definition in which Y is N-R¹ and a definition in which Y is oxygen or sulfur. Applicants submit that this amendment moots the Examiner's concern.

Claim 6 has been rejected under 35 U.S.C. §112 (second paragraph) as being indefinite for failing to define the "amount" that corresponds to successful inhibition of a condition. As noted above, claim 6 has been amended to more closely track the example language provided on pages 3-4 of the Office action. Specifically, claim 6 has been amended to remove "therapeutically effective amount". Claim 6, as amended, instead characterizes the method as

comprising the administration of the compound under conditions effective to antagonize $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin. Applicants submit that this language is definite. Under 35 U.S.C. §112 (second paragraph), claim 6 must only set out and circumscribe its subject matter with a reasonable degree of clarity and particularity. In determining whether claim 6 meets this threshold, Applicants' disclosure must be taken into account:

Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; . . .

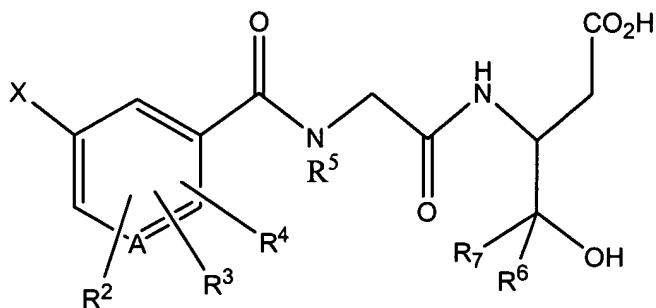
See MPEP §2173.02. As noted above, Applicants' specification provides a definition for "inhibition". Applicants' specification also provides detailed information relating to the conditions effective to antagonize $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin. One skilled in the art, especially when armed with these teachings, would be capable of defining the conditions necessary for successful inhibition of a condition mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor. This is particularly true, given the detailed description that Applicants' specification provides. As noted above, Applicants' specification, for example, provides a plethora of example diseases mediated by the $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin receptor; citations discussing various diseases associated with $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins; a detailed discussion relating to, for example, factors affecting dosages, example dosages, example modes of administration, and example adjuvants; and assays to determine potency and selectivity of a particular compound. Given this context, Applicants submit that claim 6 meets the definiteness requirement of 35 U.S.C. §112 (second paragraph).

Claim 7 has been rejected for reciting angiogenesis *per se*, including healthy angiogenesis. Claim 7 has been amended to characterize the angiogenesis as "tumor angiogenesis" in accordance with Applicants' specification at, for example, page 13, lines 10-14. Applicants submit that this amendment moots the Examiner's concern.

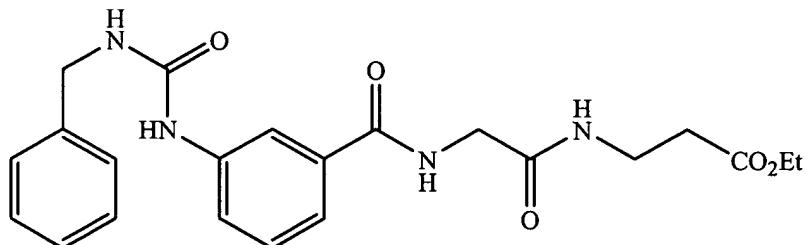
VII. Response to rejection of claim 1 under 35 U.S.C. §102(b)

Claim 1 has been rejected under 35 U.S.C. §102(b) as lacking novelty over WO 97/08145. Applicants request withdrawal of this rejection.

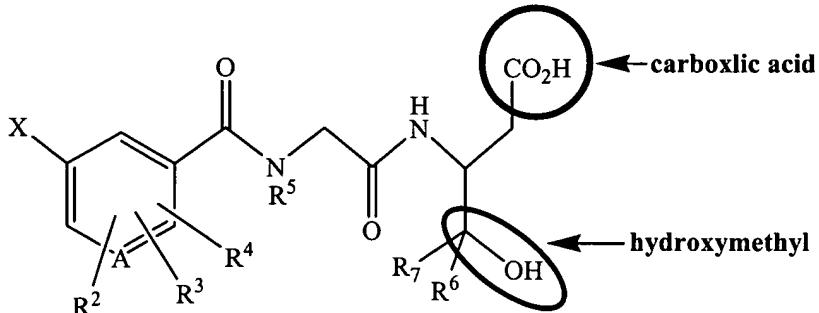
Claim 1 is directed to compounds having the following structure:



Applicants do not believe that WO 97/08145 discloses any compound species falling within this structure. For example, the Office action cites to example 102 on page 230 of WO 97/08145. That compound corresponds in structure to the following formula:



As can be seen, the structure does not comprise either the hydroxymethyl substituent or the unsubstituted carboxylic acid in the compounds of Applicants' claim 1 (circled below):



Thus, for at least these reasons, claim 1 is novel over WO 97/08145.

VIII. New claims 8-16

Each of new claims 8-16 depends directly or indirectly from claim 1, 2, 3, and/or 4. Applicants submit that each of claims 8-16 is patentable for at least the same reasons as the claims from which it directly and indirectly depends.

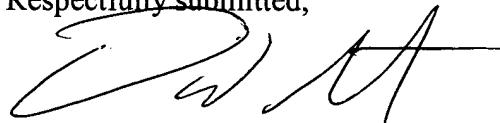
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Applicants hereby request a 3-month extension to respond to the October 4, 2004 Office action. Applicants have enclosed a check to cover the fee for the extension. Applicants believe

that they do not owe any additional fee in connection with this filing. If, however, Applicants do owe any such fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. **08-0750**. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **08-0750**.

Applicants submit that the pending claims are in condition for allowance, and request that this application be allowed. The Examiner is requested to call the Undersigned if any issues arise that can be addressed over the phone to expedite examination of this application.

Respectfully submitted,



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Appendix A
Marked-Up Version of Amendments to Specification

Please amend the paragraph bridging lines 6-8 on page 1 in the following manner:

This patent The present application claims priority under Title 35, United States Code, §119 [[of]] to United States Provisional Application applications Serial No. 60/235,616 (filed September 27, 2000) and Serial No. 60/60/241,656 60/241,656 (filed October [[10]] 19, 2000).